AMENDMENT No. 001
BAA-NIAID-DMID-NIHAI2012149
"Development of Therapeutic Medical Countermeasures for Biodefense and Emerging Infectious 'Diseases"

Solicitation Number:	**BAA-NIAID-DMID-NIHAI2012149**
Amendment Number:	**One (001)**
Amendment Issue Date:	**August 1, 2012**
Proposal Due Date:	**Monday October 1, 2012 3:30PM Local Time (UNCHANGED)**
Issued By:	**Kathy M. Fetterman** Contract Specialist Office of Acquisitions, DEA National Institute of Allergy and Infectious Diseases National Institute of Health 6700-B Rockledge Drive Room 3214, MSC 7612 Bethesda, Maryland 20892-7612
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The purpose of this amendment is as follows:

The Broad Agency Issue Date is changed from July 15, 2012 to July 17, 2012

SYNOPSIS DESCRIPTION LANGUAGE is revised as posted with this amendment 001.

QUESTIONS AND ANSWERS regarding this BAA are attached below.

The date specified for receipt of proposals is unchanged.

Offerors must acknowledge receipt of this Amendment by identifying this amendment number and date of the amendment on each copy of the offer submitted. Failure to receive your acknowledgement may result in the rejection of your offer. Except as provided herein, all terms and conditions of the solicitation remain unchanged and in full force and effect.

BAA- NIAID-DMID- NIHAI2012149
(Questions & Answers)

Development of Therapeutic Medical Countermeasures for Biodefense and Emerging Diseases

Question 1 Would a broad spectrum antibody with neutralizing activity against all four serotypes of dengue be considered responsive? Since such an antibody would cover both Dengue serotype 1 AND serotypes 2, 3, and 4, such an agent should be considered responsive to this solicitation. Do you agree with this interpretation?

Response: Yes, a therapeutic that is active against 4 serotypes of Dengue would be eligible under the broad spectrum criteria and each Dengue serotype is considered a different virus since it is known that natural infection with one serotype of Dengue virus does not confer immunity to other serotypes.

Question 2 Will a proposal submitted for influenza require an additional A, B, or C pathogen as stated in the summary or just other influenza subtypes as stated in the "big" announcement?

Response: As stated in the Technical Objectives of the BAA influenza antiviral therapeutic agents should be active against multiple influenza A subtypes directed at either viral or host targets.

Therapeutics supported under this BAA are specified as the following classes:

- ***Broad spectrum anti-bacterial: Therapeutic with activity against one of the following bacterial pathogens: Bacillus anthracis, Francisella tularensis, Yersinia pestis, Burkholderia pseudomallei, B. mallei, and Rickettsia prowazekii AND in addition, activity against one other NIAID Category A, B and C bacterial threat agent.***

- ***Broad spectrum anti-viral: Therapeutic with activity against one of the following viral pathogens: Ebola virus, Marburg virus, Variola major, Dengue virus, Venezuelan encephalitis virus, Western Equine encephalitis virus, and Eastern Equine encephalitis virus AND, in addition, activity against one other NIAID Category A, B and C viral threat agent.***

- ***Influenza antiviral agents: Therapeutics active against multiple influenza A subtypes directed at either viral or host targets.***

- ***Anti-toxins supported under this BAA are specified as the following: A therapeutic agent, particularly a small molecule, with activity against one of the following toxins: Botulinum neurotoxin, Staphylococcus enterotoxin B, Bacillus anthracis Protective Antigen, Lethal Factor or Edema Factor, and ricin toxin.***

Question 3 This project aims to provide, on a world-wide basis, complete turn-key facilities which have a high probability of stopping a global lethal viral pandemic by providing and distributing an effective live vaccine within eight weeks of an outbreak. Does this project fit anywhere into HHS biodefense or does it belong in Homeland Security? Would HHS wish to collaborate on this project? If so, who would be the best point of contact?

Response: NIAID, NIH, DHHS is sponsoring this solicitation. As stated in the Broad Agency Announcement the objectives of the solicitation is development of therapeutic candidates. Vaccines are not eligible and proposals that focus on development of vaccine platforms are also not eligible. Please refer to Section A of the BAA, excerpted below.

This BAA solicitation focuses on supporting the development of promising biodefense therapeutic candidates/products.

Question 4 Would *in vitro* effect in stabilizing cells against influenza virus and *Ex vivo* (macrophages from individuals with HIV infected) a reduction in replication of Mtb (Mycobacterium tuberculosis) in macrophage cells from humans and then infected with Mtb. data qualify us to apply for the above BAA?

Please note that the language regarding the candidate product stated in the BAA, excerpted below.

Furthermore, the candidate must meet the following criteria:

1) A drug (synthetic or natural product) or a biological product (e.g. monoclonal antibody or a recombinant protein) intended for use in the cure, mitigation, or treatment; AND
2) A single agent with demonstrated activity in appropriate in vitro assays and in vivo models against more than one selected bacterial or viral pathogen ; AND
3) An agent that will have completed evaluation in a Phase 1 clinical trial within the 5-year contract period of performance.

Therefore, a candidate agent must have demonstrated in vitro AND in vivo activity in a non-clinical treatment model of a relevant disease. As such, the observed in vitro effect in stabilizing cells against viral infection does not meet the eligibility criteria. Please also note that HIV is not included in the list of NIAID Category A, B and C threat agents.

Question 5 ***Two –Part:*** 1) Positive preliminary data in mice has been obtained indicating that activator is able to protect against a lethal anthrax bacterial infection and also a lethal NIAID Category B viral infection. Given the activity in these two systems of different classes, is it necessary to show activity against a second pathogen in one or both of these classes?

2) Activator is effective when given before (prophylactic), concurrently, or shortly after (within 24 hours) exposure to the pathogens mentioned above. It appears to be ineffective if administered more than 24 hours post-exposure to the agent. While this timing would provide adequate protection for populations if given at the time of exposure or for populations that had prior warning in the vicinity of the agent exposure, is this prophylactic/therapeutic agent profile considered responsive to the objectives of the BAA in spite of the timing limitations?

Response: Please note that the BAA solicitation calls for therapeutics to be used in treatment of disease. Candidates that are regulated under the FDA's Animal Rule will have to show a treatment effect therefore, candidates that are intended for post-exposure prophylaxis as a clinical indication are not eligible under this solicitation. Please see the relevant sections from the Technical Objectives below.

For the purposes of this BAA, the ideal broad spectrum therapeutic candidate is defined as a single agent that meets the following three criteria/definitions:
1) A drug (synthetic or natural product) or a biological product (e.g. monoclonal antibody or a recombinant protein) intended for use in the cure, mitigation, or treatment; AND
2) A single agent with demonstrated activity in appropriate in vitro assays and in vivo models against more than one selected bacterial or viral pathogen ; AND
3) An agent that will have completed evaluation in a Phase 1 clinical trial within the 5-year contract period of performance.

Contracts awarded under this BAA will not support:
- ***Basic research and discovery of new candidates/products.***
- ***Refinement of a lead series to identify a lead candidate.***
- ***Development of devices or diagnostics.***
- ***Development of candidates/products that have not demonstrated activity in a relevant animal model of disease.***

Question 6 Since COX-2 inhibitors are already FDA-approved, is this something NIH would be interested in supporting?

Please note that the BAA solicitation calls for therapeutics to be used in treatment of disease. Candidates that are regulated under the FDA's Animal Rule will have to show a treatment effect therefore, candidates that are intended for post-exposure prophylaxis as a clinical indication are not eligible under this solicitation. Please see the relevant sections from the Technical Objectives below.

For the purposes of this BAA, the ideal broad spectrum therapeutic candidate is defined as a single agent that meets the following three criteria/definitions:

1) A drug (synthetic or natural product) or a biological product (e.g. monoclonal antibody or a recombinant protein) intended for use in the cure, mitigation, or treatment; AND

2) A single agent with demonstrated activity in appropriate in vitro assays and in vivo models against more than one selected bacterial or viral pathogen ; AND

3) An agent that will have completed evaluation in a Phase 1 clinical trial within the 5-year contract period of performance.

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- ***Basic research and discovery of new candidates/products.***
- ***Refinement of a lead series to identify a lead candidate.***
- ***Development of devices or diagnostics.***
- ***Development of candidates/products that have not demonstrated activity in a relevant animal model of disease.***

Question 7 Please clarify whether therapeutic candidates/products for this call HAVE to be broad spectrum?

Response: The anti-toxin therapeutics being requested under this solicitation do not have to be broad-spectrum.

- ***Anti-toxins supported under this BAA are specified as the following: A therapeutic agent, particularly a small molecule, with activity against one of the following toxins: Botulinum neurotoxin, Staphylococcus enterotoxin B, Bacillus anthracis Protective Antigen, Lethal Factor or Edema Factor, and ricin toxin.***

However, all other classes of therapeutics must be broad-spectrum as defined in the technical objectives:

- ***Broad spectrum anti-bacterial: Therapeutic with activity against one of the following bacterial pathogens: Bacillus anthracis, Francisella tularensis, Yersinia pestis, Burkholderia pseudomallei, B. mallei, and Rickettsia prowazekii AND in addition, activity against one other NIAID Category A, B and C bacterial threat agent.***

- ***Broad spectrum anti-viral: Therapeutic with activity against one of the following viral pathogens: Ebola virus, Marburg virus, Variola major, Dengue virus, Venezuelan encephalitis virus, Western Equine encephalitis virus, and Eastern Equine encephalitis virus AND, in addition, activity against one other NIAID Category A, B and C viral threat agent.***

- ***Influenza antiviral agents: Therapeutics active against multiple influenza A subtypes directed at either viral or host targets.***

Question 8 Considering the appalling situation mother nature has done to our Gram-negative antibiotics and there is not much coming through to treat these, is NIAID interested in a proposal on FabI inhibitors?

Response: As stated in the BAA, anti-bacterial therapeutics supported under this BAA are specified as:

- ***Broad spectrum anti-bacterial: Therapeutic with activity against one of the following bacterial pathogens: Bacillus anthracis, Francisella tularensis, Yersinia pestis, Burkholderia pseudomallei, B. mallei, and Rickettsia prowazekii AND in addition, activity against one other NIAID Category A, B and C bacterial threat agent.***

Furthermore, the candidate must meet the following criteria:

1) ***A drug (synthetic or natural product) or a biological product (e.g. monoclonal antibody or a recombinant protein) intended for use in the cure, mitigation, or treatment; AND***
2) ***A single agent with demonstrated activity in appropriate in vitro assays and in vivo models against more than one selected bacterial or viral pathogen ; AND***
3) ***An agent that will have completed evaluation in a Phase 1 clinical trial within the 5-year contract period of performance.***

Therefore, if a candidate agent has demonstrated in vitro and in vivo activity against one of the biothreat bacterial pathogens (such as B. anthracis, F. tularensis or R. prowazekii) as well as activity against one other NIAID Category A, B and C bacterial pathogen and it is indicated for treatment and will be able to complete phase I evaluation within a 5 year period of performance, then it meets the eligibility criteria for this solicitation. Please refer to the NIAID list of priority pathogens and note that anti-microbial resistant strains of bacterial pathogens are included under Category C.
http://www.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/Pages/CatA.aspx

Question 9 Do Category A agents in this announcement include smallpox. Is funding to advance a very promising smallpox drug available under this BAA?

Response: As stated in the Technical Objectives of the BAA an anti-viral agent that is active against Variola major (i.e. the agent that causes smallpox) must also show activity against one other NIAID Category A, B, or C viral threat agent. If the drug being referenced is only active again Variola major, it is not eligible under this solicitation.

Therapeutics supported under this BAA are specified as the following classes:

- ***Broad spectrum anti-bacterial: Therapeutic with activity against one of the following bacterial pathogens: Bacillus anthracis, Francisella tularensis, Yersinia pestis, Burkholderia pseudomallei, B. mallei, and Rickettsia prowazekii AND in addition, activity against one other NIAID Category A, B and C bacterial threat agent.***

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Anti-toxins supported under this BAA are specified as the following: A therapeutic agent, particularly a small molecule, with activity against one of the following toxins: Botulinum neurotoxin, Staphylococcus enterotoxin B, Bacillus anthracis Protective Antigen, Lethal Factor or Edema Factor, and ricin toxin.

Question 10 The NIAID is interested in supporting the development of promising biodefense therapeutic and prophylactic (vaccine) candidates/products with the eventual goal of stockpiling these medical countermeasures and associated technologies to protect the American public.
...
Offerors are encouraged to apply state-of-art and innovative technological approaches and platforms in the development of the proposed candidates. State-of-art and innovative technological approaches refer to capabilities, such as temperature stabilization or delivery method, that can be engineered into a wide array of existing and candidate products to enhance the product performance." **I just wanted to ask specifically whether vaccine adjuvants are appropriate for this announcement?**

Response: The reference to therapeutic and prophylactic (vaccine) candidates/products was included to provide background of the overall mission of NIAID. However, the BAA announcement goes on to specify that only therapeutic candidates will be considered for this solicitation. Therefore, adjuvants for vaccines are not being considered.

"The objective of this solicitation is to support the development of candidate therapeutic products for use in post-event settings following the intentional release of the NIAID Category A, B, and C biothreat agents or in response to naturally occurring outbreaks of infectious diseases caused by the NIAID Category A, B, and C pathogens. Only agents identified as the NIAID Category A, B and C Priority Pathogens are eligible as proposed candidates/products for this solicitation.

This Broad Agency Announcement (BAA) specifically focuses on supporting the development of promising biodefense therapeutic candidates/products with broad spectrum therapeutic activity against viruses or bacterial pathogens. This solicitation also focuses on supporting development of promising anti-toxins as biodefense therapeutic candidates/products, particularly small molecule therapeutics with anti-toxin activity. The research and development activities supported through this BAA will allow candidate therapeutic countermeasures to progress through the product development pipeline toward licensure by the FDA.

Question 11 Please clarify if this BAA only supports pre-clinical to end of phase 1 activities or will it support later stage clinical development?

Response: This BAA does not support products that have already progressed through preclinical development and completed phase 1 clinical testing.

Question 12 Is the one other priority pathogen Category A only? or could it derive from A, B or C category?

Response: As stated in the BAA, Broad spectrum anti-viral is defined as a therapeutic with activity against one of the following viral pathogens: Ebola virus, Marburg virus, Variola major, Dengue virus, Venezuelan encephalitis virus, Western Equine encephalitis virus, and Eastern Equine encephalitis virus AND, in addition, activity against one other NIAID Category A, B and C viral threat agent.

Question 13 There is a requirement showing some kind of efficacy in an animal model of some kind. Does this efficacy have to be against the Ebola/Marburg, the Dengue or the Equine Encephalitis viruses? or can it involve the other pathogen? We have animal data with pre- and post-exposure prophylaxis against at least one other priority pathogen, but not animal data against the Ebola/Marburg, Dengue or Equine Encephalitis viruses at the present time.

Response: Please note that the agent must have demonstrated therapeutic activity in an animal model (see above). Agents that are only active as pre- and post-exposure prophylaxis do not meet the eligibility criteria. Please also note that the requirement is for a single agent with demonstrated activity in appropriate in vitro assays and in vivo models against more than one selected bacterial or viral pathogen. This can be interpreted as in vitro and in vivo activity against one pathogen and in vitro activity against the second pathogen. One of the two pathogens must be Ebola virus, Marburg virus, Variola major, Dengue virus, Venezuelan encephalitis virus, Western Equine encephalitis virus, or Eastern Equine encephalitis virus.

Question 14 What do you imagine the reasonable budget level to be under this BAA?

Response: As stated in Section I. INTRODUCTION of the BAA document that's attached to the Solicitation: NIAID estimates that one or more contracts may be issued for an aggregate total cost (direct and indirect costs combined) of up to $18.5 million for all awards during the first non-severable phase.

Question 15 If a collaborator is at NIAID, is it correct to assume that the collaborator **cannot** receive funds from the contract awarded under the BAA since he is an intramural NIAID investigator?

Response: Correct, an NIAID investigator cannot receive funds from this BAA.

END OF AMENDMENT NO. 001, BAA-NIAID-DMID-NIHAI2012149